#8

ORIGINAL CONTRIBUTION

Nosocomial Transmission of Highly Resistant Microorganisms on a Spinal Cord Rehabilitation Ward

Erik Slim, MD[1]; Christof A. Smit, MD[2]; Arthur J. Bos, MD, PhD[3]; Paul G. Peerbooms, MD, PhD[3]

[1]Academic Medical Center, Amsterdam, The Netherlands; [2]Spinal Cord Unit, Rehabilitation Center, Amsterdam, The Netherlands; [3]Laboratory of Microbiology, Sint Lucas Andreas Hospital, Amsterdam, The Netherlands

Received January 20, 2009; accepted March 13, 2009

Abstract

Background/Objective: To study the mechanism of nosocomial transmission of highly resistant microorganisms (HRMOs).

Design: A prospective observational study.

Setting: A spinal cord ward of a rehabilitation center.

Participants: Patients admitted to the spinal cord rehabilitation ward.

Outcome Measures: HRMOs present in urine and feces. HRMOs, Enterobacteriaceae: (1) that produced an extended-spectrum β-lactamase (ESBL), (2) that were resistant to carbapenems, (3) that fluoroquinolones and aminoglycosides (for *Escherichia coli* and Klebsiella species), or other Enterobacteriaceae species that were resistant to 2 of 3 of the following types of antibiotics (fluoroquinolones, aminoglycosides, cotrimoxazole).

Methods: Bacterial growth, identification and sensitivity were tested in urine cultures of 46 patients and faeces cultures of 15 patients. Data were collected on demographic characteristics, underlying diseases, reason and date of admission, room number, method of catheterization (suprapubic, clean intermittent catheterization or indwelling Foley catheter) and antibiotic use.

Results: Nine different HRMOs (7 *E coli*, 1 *Enterobacter cloacae*, and 1 *Citrobacter koseri*) were isolated in urine samples from 15 patients. *E coli* resistant to gentamicin, tetracycline, amoxicillin, cotrimoxazole, and ciprofloxacin were isolated from 8 patients during the study (cluster 1). One strain of multiresistant *E coli* found before the start of the study was not found during the study period (cluster 2). *E coli* strains producing an ESBL and resistant to tetracycline, cotrimoxazole, and ciprofloxacin were isolated from urine samples of 3 patients (cluster 3). Ciprofloxacin-resistant *E coli* were present in feces of 3 patients (2 in cluster 1). Catheterization was found to be significantly more prevalent in patients with HRMOs. Most of the patients in cluster 1 were treated with antibiotics before the first isolation of the strain.

Conclusions: HRMOs from urine samples were strongly correlated with the use of catheterization. A close correlation was found between prior use of antibiotics and colonization of the urinary tract on the level of the individual patient, which has been rarely described in the literature.

J Spinal Cord Med. August 2009;32(4):422–427

Key Words: Spinal cord injuries; Antibiotic resistance; Bacteriuria; Nosocomial infections; Catheterization, urinary; Fluoroquinolones; Aminoglycosides; Cotrimoxazole

INTRODUCTION

Significant bacteriuria is very prevalent in patients with spinal cord injury (SCI), especially when spontaneous micturition is not possible and the patients use permanent or intermittent catheterization for voiding (1–3). The major contributing factors are impaired voiding and subsequently impaired elimination of bacteria from the bladder in combination with colonization of permanent catheters or the introduction of bacteria from the urethral meatus and urethra into the bladder by intermittent catheterization.

Bacteriuria per se is not an indication for antibiotic treatment (2,4). Signs and symptoms of urinary tract infection are often obscured, absent, or unreliable in this population (4,5). The decision to treat a patient with SCI

Please address correspondence to Erik Slim, MD, Department of Rehabilitation, Academic Medical Center Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands; p: 003 120 566 4049; f: 003 120 566 9154 (e-mail: f.j.slim@amc.uva.nl).

for a suspected urinary tract infection is therefore dependent on indirect symptoms such as bladder spasms, newly developed or increasing urinary incontinence, unexplained fever, or autonomic dysreflexia. Antibiotic resistance is common in patients with SCI in rehabilitation centers. Most patients with SCI who are admitted to a rehabilitation center have been hospitalized previously for acute care and have received antibiotic therapy (6,7). Exposure to antibiotics has been associated with the occurrence of hospital-acquired infections in these patients (3). As a consequence they are frequently already colonized with resistant organisms on admittance.

In the first months of 2006, we noticed the isolation of *Escherichia coli* strains resistant to gentamicin, ciprofloxacin, cotrimoxazole, tetracycline, and amoxicillin from urine samples of several patients with SCI. By chart review, 8 patients were identified, and the isolates were sent to a reference laboratory for typing by pulsed-field gel electrophoresis (PFGE). Two clusters of 5 (cluster I) and 3 (cluster II) identical isolates were found and could be distinguished phenotypically by small but reproducible differences in inhibition zone sizes around cefuroxime and ceftazidime disks in disk diffusion tests.

In the rehabilitation center, urine cultures were only requested on admission to screen for the presence of multiresistant microorganisms and immediately before starting antimicrobial therapy for a presumed symptomatic urinary tract infection. No routine urine cultures were performed. Because the isolates belonging to these clusters had not been observed in admission cultures, nosocomial transmission was highly probable. This prompted us to start a prospective study to investigate how transmission of resistant bacteria was taking place in this ward and what preventive actions might be undertaken.

METHODS

Setting

This study was performed at a university-affiliated rehabilitation center in The Netherlands with a capacity of 84 beds. The rehabilitation center provides primary rehabilitation treatment and specialized (tertiary) spinal cord rehabilitation treatment. The spinal cord unit is a 36-bed ward for patients with SCI and spinal cord–related medical problems. The spinal cord ward consists of different subunits: 4 units with 4 beds, 9 units with 2 beds, and 4 units with 1 bed. Toilets and showers are equally shared by patients.

Study Design

This study was a prospective observational study of patients admitted to the spinal cord rehabilitation ward during a 3-month period from July through October 2006. Urine samples were obtained from all patients already present at the ward at the start of the study and of the new admitted patients during the study period. Urine samples were routinely collected on admittance and every second week. Data collected from the medical records/charts included information on demographic characteristics, underlying diseases, reason for admission to the unit, date of admission, room number, method of catheterization in case of impaired micturition (suprapubic [SP], clean intermittent catheterization [CIC], or an indwelling Foley catheter [FC]), and antibiotic use.

Patients

All patients admitted to the spinal cord ward during the period were included in this study if at least 2 consecutive urine samples were obtained. Diagnoses included acute and chronic SCI, multitrauma, Guillain Barré, and transverse myelitis.

Urine Cultures

Urine samples were collected from all patients in the ward using a clean-catch technique for patients able to void, at the time of intermittent catheterization, or from an FC or SP catheter in accordance with guidelines established by the rehabilitation unit. Urine specimens were kept at 4°C until (daily) transport to the microbiologic laboratory. Urine samples were cultured on chromogenic agar medium enabling the recognition of different Enterobacteriaceae (CPS-ID2; bioMérieux, Marcy l'Etoile, France), a blood agar with colistin and aztreonam for gram-positive organisms, and cytine-lactose-electrolyte deficient (CLED) agar. In addition, Mueller-Hinton agar with antibiotic disks (Neosensitab-disk; Rosco, Taastrup, Denmark) was inoculated directly with the urine sample to enable detection of resistant organisms. Identification of Enterobacteriaceae by API 20E (bioMerieux) and sensitivity testing by disk diffusion methods for individual isolates were performed where indicated.

Bacterial growth was classified as follows—greater than 10^4 CFU/mL of a single species: significant growth, identification and susceptibility testing of the isolate were performed; greater than 10^4 CFU/mL mixed growth with gram-negative rods predominating: significant growth, a resistance pattern of a mixture of the gram-negative rods was obtained, if there was an indication for the presence of an extended-spectrum β-lactamase (ESBL) or resistance for gentamicin or ciprofloxacin, identification and a resistance pattern of the resistant isolate was obtained; all other growth patterns: nonsignificant. Because we were especially interested in the transmission of (resistant) gram-negative rods, the presence of these bacteria in lower numbers than 10^4 CFU/mL was recorded. The presence of mixed growth (also when $>10^4$ CFU/mL) of gram-positive bacteria such as enterococci, coagulase-negative staphylococci, diphtheroids, and lactobacilli was recorded but not considered significant.

Table 1. Antibiotic Use, Catheter Type, and Culture Results of Urine Samples From Patients With SCI

Catheterization Type	No. of Patients	No. of Patients With HRMOs (%)	No. of Urine Samples	No. (%) With Significant Growth	No. of Samples/ Patients With HRMOs	No. of Antibiotic Treatments/Patients
No catheter	18	1 (6%)	65	11 (17%)	4/1	2/1
Yes (CIC, FC, SP)	28	14 (50%)	137	117 (85%)	50/14	17/13
CIC	9	5 (56%)	43	38 (88%)	11/5	6/6
FC	10	4 (40%)	48	38 (79%)	14/4	8/5
SP	9	5 (56%)	46	41 (89%)	25/5	3/2
Total	46	15 (33%)	202	128 (63%)	54/15	19/14

CIC, clean intermittent catheterization; FC, Foley catheter; SP, suprapubic catheter; and HRMO, highly resistant microorganism.

Antibiotic Resistance

We used the definition given by the Dutch Working Party on Infection Prevention (WIP) for highly resistant microorganisms (HRMOs) (8). Isolates belonging to the family of Enterobacteriacea that produced an ESBL, were resistant to carbapenems, or were resistant to fluoroquinolones and aminoglycosides (for *E coli* and Klebsiella species), were considered highly resistant, as were other species that were resistant to 2 out of 3 of the following classes of antibiotics (fluoroquinolones, aminoglycosides, and cotrimoxazole).

Antimicrobial Therapy

All patients admitted to the unit during the study were monitored for therapy with antibiotics (except topical antimicrobial therapy). The antibiotic policy in cases of urinary tract infection was to restrict the use of antibiotics and only start antibiotic treatment when clinical symptoms (mentioned above) were clearly present. Antibiotics used were traced back until 3 months before the first HRMO-positive culture. Antibiotics used more than 3 months before the first positive culture with HRMOs were not considered relevant. This was done for all patients present during the 3-month study period.

Fecal Carriage of Ciprofloxacin-Resistant *E coli*

After conclusion of the study period, rectal swabs were collected from 15 patients from the SCI ward in November 2006. Swabs were cultured overnight in tryptic soy broth containing ciprofloxacin (1 mg/L); the broth was subcultured on CPS-ID2 medium with a ciprofloxacin disk. Antibiotic susceptibility was tested for suspected ciprofloxacin-resistant *E coli* growing as red colonies near the disk.

Molecular Typing

PFGE typing was performed at the National Institute of Public Health (RIVM) for the isolates obtained before the study; ligation-mediated polymerase chain reaction (LM-PCR) was used to confirm the clonality of highly resistant *E coli* strains with similar resistance patterns obtained during the study period (Dr. P.H.M. Savelkoul, Vrije Universiteit, Amsterdam, The Netherlands).

Statistical Analysis

In general, the unit of analysis is the patient with or without a catheter. The proportions of patients with highly resistant microorganisms or receiving antibiotic treatment with any kind of catheterization were compared with patients without a urinary catheter. Quantitative variables in the different patients groups were compared using the Fisher's exact test. Also, the percentage of urine samples with significant growth in patients with a catheter were compared with the percentage of urine samples with significant growth in patients without a catheter (Fisher's exact test).

RESULTS

Patient Characteristics and Culture Results

Forty-six patients (16 women; mean age, 52.7 years; range, 24–83 years) were included in the study. Details on type of catheterization, number of urine samples, and culture results are presented in Table 1. Significant growth in urine samples, isolation of highly resistant organisms, and antibiotic treatment were all significantly more prevalent in patients with any kind of catheterization compared with patients without a urinary catheter ($P < 0.01$, Fisher's exact test [patients and for samples]).

Isolation of Highly Resistant Bacteria From Urine Samples

HRMOs were isolated from 15 patients (7 *E coli*, 1 *Enterobacter cloacae*, and 1 *Citrobacter koseri*); 7 were only isolated from 1 individual patient each, and 2 were isolated from more than 1 patient. Eleven patients (93%) with HRMOs used antibiotics compared with only 4 patients (27%) with HRMOs who did not.

Fourteen (50%) of the 28 patients with some form of catheterization were positive for HRMOs; 11 of the 28 patients (39%) used antibiotics. One (6%) of 18 patients without catheterization was positive for HRMO and used antibiotics before the positive culture (Table 1). Epidemic strains of *E coli* belonging to cluster I (resistant to

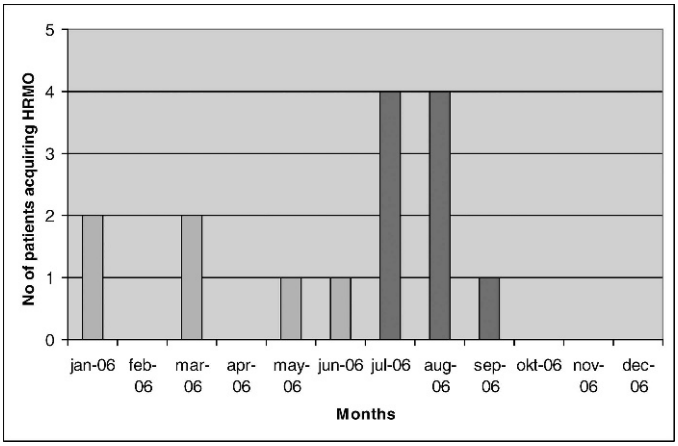

Figure 1. *Epidemic curve of HRMOs in patients before, during, and after the study period. The study period is dark gray.*

gentamicin, tetracycline, amoxicillin, cotrimoxazole, and ciprofloxacin) were isolated from 8 patients during the study, 4 of whom were already known to harbor this strain before the study period. The first isolation of a strain belonging to this cluster occurred in December 2005, and occasionally new patients were still being identified as harboring this strain in urine samples collected after the study period (Figure 1).

Epidemic strains belonging to cluster II were not found during the study period. Epidemic *E coli* strains, belonging to a third cluster (III), producing an ESBL and resistant to tetracycline, cotrimoxazole, and ciprofloxacin, were isolated from urine samples of 3 patients. Eight of the 9 patients with an epidemic *E coli* strain (clusters I and III) had received at least 1 antibiotic course in a period from 2 weeks to 3 months before the first positive culture. In comparison, of the 18 patients with some form of catheterization in which the epidemic strain was not isolated, only 8 received an antibiotics course in the 3 months of the study ($P = 0.04$, Fisher's exact test). Data concerning the date of the first urine sample with an epidemic *E coli* strain (clusters I and III), date of previous urine culture, and previous antibiotic treatment(s) are shown in Table 2.

Fecal Carriage of Ciprofloxacin-Resistant *E coli*

Rectal swabs were obtained from 15 patients after informed consent to test for the presence of ciprofloxacin-resistant *E coli*. Three patients tested positive, 2 of whom carried the epidemic cluster I strain. The third patient carried a ciprofloxacin-resistant *E coli*, which was shown to be identical by LM-PCR to an isolate from a urine sample from another patient 2 months earlier.

DISCUSSION

Being confronted with convincing evidence for transmission of HRMOs in patients in the rehabilitation center, we questioned whether this transmission could be prevented by hygienic precautions. In the guidelines issued by the Dutch Working Party on Infection Prevention, contact isolation in a single room is recommended in case of an outbreak with highly resistant Enterobacteriaceae. This was not considered feasible because it would seriously interfere with the rehabilitation process. We decided to start a prospective study hoping that by routinely culturing urine samples from all patients in the ward in combination with recording possible relevant data, we might be able to identify the variables that were important for sustaining transmission.

As expected, significant bacteriuria was much more frequently detected in patients with some form of catheterization than in patients with spontaneous micturition ($P < 0.01$). No significant difference was seen in the percentage of patients with significant bacteriuria between different forms of catheterization. The isolation of highly resistant bacteria from urine samples was also

Table 2. Acquisition of an Epidemic HRMO (Clusters I and III)

Patient	Cluster Type	Date of Admission	Date of First Isolation	Date of Previous Culture	Antimicrobial Therapy/Period
1	I	07/27/2006	08/14/2006	07/31/2006	AMC August 2006
2	I	05/23/2006	07/10/2006	NA	CIP /07/07/2006–07/14/2006
3	I	02/27/2006	07/10/2006	07/03/2006	>3 months
3	III	02/27/2006	07/03/2006	05/01/2006	>3 months
4	I	11/03/2005	03/01/2006	02/07/2006	CIP 12/20/2006–12/27/2006
5	I	05/18/2006	08/11/2006	07/31/2006	CIP 7/20/2006–7/28/2006
6	III	06/23/2005	07/17/2006	NA	CIP 4/13/2006–4/26/2006
7	I	07/06/2005	03/08/2006	10/13/2005	FLU 12/14/2005–2/8/2006
8	I	04/26/2006	05/16/2006	04/27/2006	COT 05/04/2006–05/09/2006
9	III	05/02/2006	07/31/2006	07/17/2006	AMC 4/13/2006–5/1/2006
9	I	05/02/2006	06/30/2006	06/15/2006	AMC 4/13/2006–5/1/2006

NA, not available; CIP, ciprofloxacin; COT, cotrimoxazole; AMC, amoxicillin clavulanate potassium; CLA, clarithromycin; FLU, flucloxacillin; and HRMO, highly resistant microorganism.

strongly correlated to the use of some form of catheterization. Finally, the isolation of an epidemic strain of a highly resistant *E coli* from a urine sample was almost always related to antibiotic treatment in the preceding weeks or months. Significantly more patients with the epidemic strains of HRMO used antibiotics before the first positive culture ($P = 0.04$).

On the SCI ward, 38 patients live in close proximity to each other and share sanitary facilities. This situation is comparable to an extended household. Transmission of fecal bacteria in a household setting is common (9). Without antibiotic therapy, it is unlikely for contaminating bacteria to successfully establish themselves in the intestinal tract. However, when the intestinal flora is disturbed by the use of antibiotics, especially those that reach high levels in the intestinal lumen, a niche is created for resistant organisms to establish themselves as dominant organism in the gut. From there, they will colonize the periurethral area and can be introduced in the bladder by catheterization.

Our findings are completely consistent with this hypothesis. We found a clear correlation between the use of antibiotics and subsequently colonization of urine with HRMOs. We were able to show the presence of a distinct clone of a multiresistant *E coli* (cluster I) in the feces of patients on the SCI ward. This same *E coli* was found as the predominant microorganism in the urine of 8 patients in this ward in the 3-month study period. The same strain was isolated for the first time 6 months before this study and has been isolated occasionally after this period, bringing the total number of patients with this strain in a urine sample to 16, all of them using some form of catheterization and most of them being treated with antibiotics before the first isolation of this strain.

Previous antibiotic use has been described as a risk factor for the acquisition of multiresistant *E coli* strains in hospitalized patients (10,11). Antibiotic therapy has been shown to promote proliferation of antibiotic-resistant microorganisms by exerting selective pressure (ie, inhibition of competing microflora but not of resistant organisms) (12). The colonization of the perineum and urethra with ciprofloxacin-resistant bacteria after treatment with ciprofloxacin has also been described (13). The flora of the anterior urethra is strongly correlated to that of the perineum as well as that of the urethral meatus and the bladder. (13–15). Mathur et al (16) suggested that fecal strains contaminate the perineum and urethral meatus and ascend to the bladder along the external catheter surface. However, the close correlation between prior antibiotic use and the colonization of the urinary tract with the same multiresistant strain on the level of individual patients has rarely been described. Fecal–oral transmission is inevitable in rehabilitation centers as is also shown by the numerous reports of outbreaks of norovirus in institutions (17). It is difficult to imagine how this can be prevented by hygienic measures alone, given the architectural design of shared rooms and sanitary facilities. The decisive factor enabling these resistant bacteria to become established in high numbers in the fecal flora and subsequently colonize the urinary tract is most likely the use of antibiotics. Managing the problem of transmission of multiresistant microorganisms remains a challenge, given the almost universal presence of significant bacteriuria in patients using some form of catheterization and the difficult relationship between bacteriuria and clinical symptoms.

ACKNOWLEDGMENTS

The authors thank the Dutch Working Party on Infection Prevention for their advice and recommendations, P.H.M. Savelkoul, MD, PhD, Vrije Universiteit Amsterdam, for the ligation-mediated PCR, and the National Institute of Public Health (RIVM) for the pulsed field gel electrophoresis typing.

REFERENCES

1. Cardenas DD, Hooton TM. Urinary tract infection in persons with spinal cord injury. *Arch Phys Med Rehabil.* 1995;76(3):272–280.
2. Penders J, Huylenbroeck AAY, Everaert K, van Laere M, Verschraegen GLC. Urinary infections in patients with spinal cord injury. *Spinal Cord.* 2003;41(10):549–552.
3. Evans CT, LaVela SL, Weaver FM, et al. Epidemiology of hospital-acquired infections in veterans with spinal cord injury and disorder. *Infect Control Hosp Epidemiol.* 2008; 29(3):234–242.
4. Waites KB, Canupp KB, DeVivo MJ. Epidemiology and risk factors for urinary tract infection following spinal cord injury. *Arch Phys Med Rehabil.* 1993;74(7):691–695.
5. Linsenmeyer TA, Oakley A. Accuracy of individuals with spinal cord injury at predicting urinary tract infections based on their symptoms. *J Spinal Cord Med.* 2003;26(4):352–357.
6. Mylotte JM, Kahler L, Graham R, Young L, Goodnough S. Prospective surveillance for antibiotic-resistant organisms in patients with spinal cord injury admitted to an acute rehabilitation unit. *Am J Infect Control.* 2000;28(4):291–297.
7. Mylotte JM, Graham R, Kahler L, Young L, Goodnough S. Epidemiology of nosocomial infection and resistant organisms in patients admitted for the first time to an acute rehabilitation unit. *Clin Infect Dis.* 2000;30(3):425–432.
8. Kluytmans-Vandenbergh MF, Kluytmnas JA, Voss A. Dutch guideline for preventing nosocomial transmission of highly resistant microorganismes. *Infection.* 2005;33(5–6):309–313.
9. Johnson JR, Owens K, Gajewski A, Clabots C. *Escherichia coli c*olonization patterns among human household members and pets, with attention to acute urinary tract infection. *Clin Infect Dis.* 2008;197(2):218–224.
10. Van der Zwet WC, Van Riessen N, Bergervoet PW, Van der Laan JR, Savelkoul PH, Sebens FW. Outbreak of multi-resistant Escherichia coli on a surgical ward: course, measures and consequences for future admissions of contaminated patients. *Ned Tijdschr Geneeskd.* 2005;149(41):2281–2286.
11. Rodriquez-Baño J, Navarro MD, Romero L, et al. Clinical and molecular epidemiology of extended-spectrum beta-lactamase-producing Escherichia coli as a cause of nosocomial infection or colonization: implications for control. *Clin Infect Dis.* 2006;42(1):37–45.

12. Donskey CJ. Antibiotic regimens and intestinal colonization with antibiotic-resistant gram-negative bacilli. *Clin Infect Dis.* 2006;43(suppl 2):S62–S69.
13. Waites KB, Canupp KC, Brookings ES, DeVivo MJ. Effect of oral ciprofloxacin on bacterial flora of perineum, urethra, and lower urinary tract in men with spinal cord injury. *J Spinal Cord Med.* 1999;22(3):192–198.
14. Barnes DG, Timoney AG, Moulas G, Shaw PJ, Sanderson PJ. Correlation of bacteriological flora of the urethra, glans and perineum with organisms causing urinary tract infection in the spinal injured male patient. *Paraplegia.* 1992;30(12): 851–854.
15. Waites KB, Canupp KC, DeVivo MJ. Microbiology of the urethra and perineum and its relationship to bacteriuria in community-residing men with spinal cord injury. *J Spinal Cord Med.* 2004;27(5):448–452.
16. Mathur S, Sabbuba NA, Suller MTE, Stickler DJ, Feneley RCL. Genotyping of urinary and fecal Proteus mirabilis isolates from individuals with long-term urinary catheters. *Clin Microbiol Infect Dis.* 2005;24(9):643–644.
17. Hansen S, Stamm-Balderjahn S, Zuschneid I, et al. Closure of medical departments during nosocomial outbreaks: data from a systematic analysis of the literature. *J Hosp Infect.* 2007;65(4):348–353.